EDITORIAL

Evaluating the severity of aortic stenosis: a re-look at our current 'gold standard' measurements

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Online publish-ahead-of-print 27 April 2018

This editorial refers to 'Pressure gradient vs. flow relationships to characterize the physiology of a severely stenotic aortic valve before and after transcatheter valve implantation'[†], by N.P. Johnson *et al.*, on page 2646.

The decision to treat a patient with aortic stenosis (AS) is dependent upon the presence or absence of symptoms and the severity of stenosis. Both the ESC and ACC/AHA Guidelines now define severe AS as a mean gradient ≥40 mmHg and aortic valve area (AVA) ≤1.0 cm^2, and cardiologists are routinely applying these 'cut-off' values to all patients with AS. However, in clinical practice, there remain patients who may not fall into these discrete haemodynamic categorizations, such as the patient with an AVA <1.0 cm^2 but a low gradient, as well as the symptomatic patient with suspected severe AS but calculated AVA >1.0 cm^2. It is thus important to re-examine critically the derivation and limitation of these values, particularly the AVA.

The aortic valve area

Gorlin *et al.* originally proposed their valve area formula in 1951, developed in only 11 patients with mitral stenosis, and it was highly theoretical since transvalvular gradients were not available.[1] This formula was then extrapolated to the aortic valve and has been accepted as the gold standard for severity of AS. The acceptance of the continuity AVA equation by Doppler echocardiography by the cardiology community was subsequently based upon its validation with the Gorlin equation.[2] However, simplifying assumptions are present when using the Gorlin equation for calculating an AVA including (i) assuming a fixed orifice area and constant flow rate throughout ejection; (ii) ignoring the inertia to opening from a thickened and stenotic valve; (iii) ignoring pulsatile arterial and valvular load; (iv) using a constant value in the formula which ignores frictional velocity loss and orifice contraction constants;[3] and (v) assuming a quadratic relationship between flow and the pressure gradient.[4,5] Given the frequent discordance observed in AS severity classification,[6] it stands to reason that these assumptions have introduced clinically significant error. In particular, the quadratic pressure–flow relationship has been questioned, leading some to propose a simpler aortic valve resistance index using a linear pressure–flow relationship.[4,5,7]

The pressure–flow relationship in aortic stenosis

To settle this debate, Johnson *et al.*[8] performed an elegant study among 16 patients with unequivocally severe AS (mean valve area 0.5 cm^2, mean gradient 45 mmHg) which is reported in this issue of the journal. Using high fidelity micromanometer pressure, they calculated a Gorlin valve area both before and after dobutamine and repeated their measurements after transcatheter aortic valve implantation (TAVI). The authors observed no correlation between changes in transvalvular flow and pressure gradient using either the Gorlin quadratic assumption or the aortic valve resistance linear model, demonstrating that both models were flawed. In contrast, after TAVI (which removed the AS-related load from the ventricle), there was a remarkable perfectly linear pressure–flow relationship indicating that a normally functioning prosthetic valve results in a steady-state resistance. They also demonstrated that in contrast to resting measures, the stress-related valve gradient and a new aortic/left ventricular systolic pressure ratio (valvular fractional flow reserve) correlated very well with flow improvement post-TAVI.
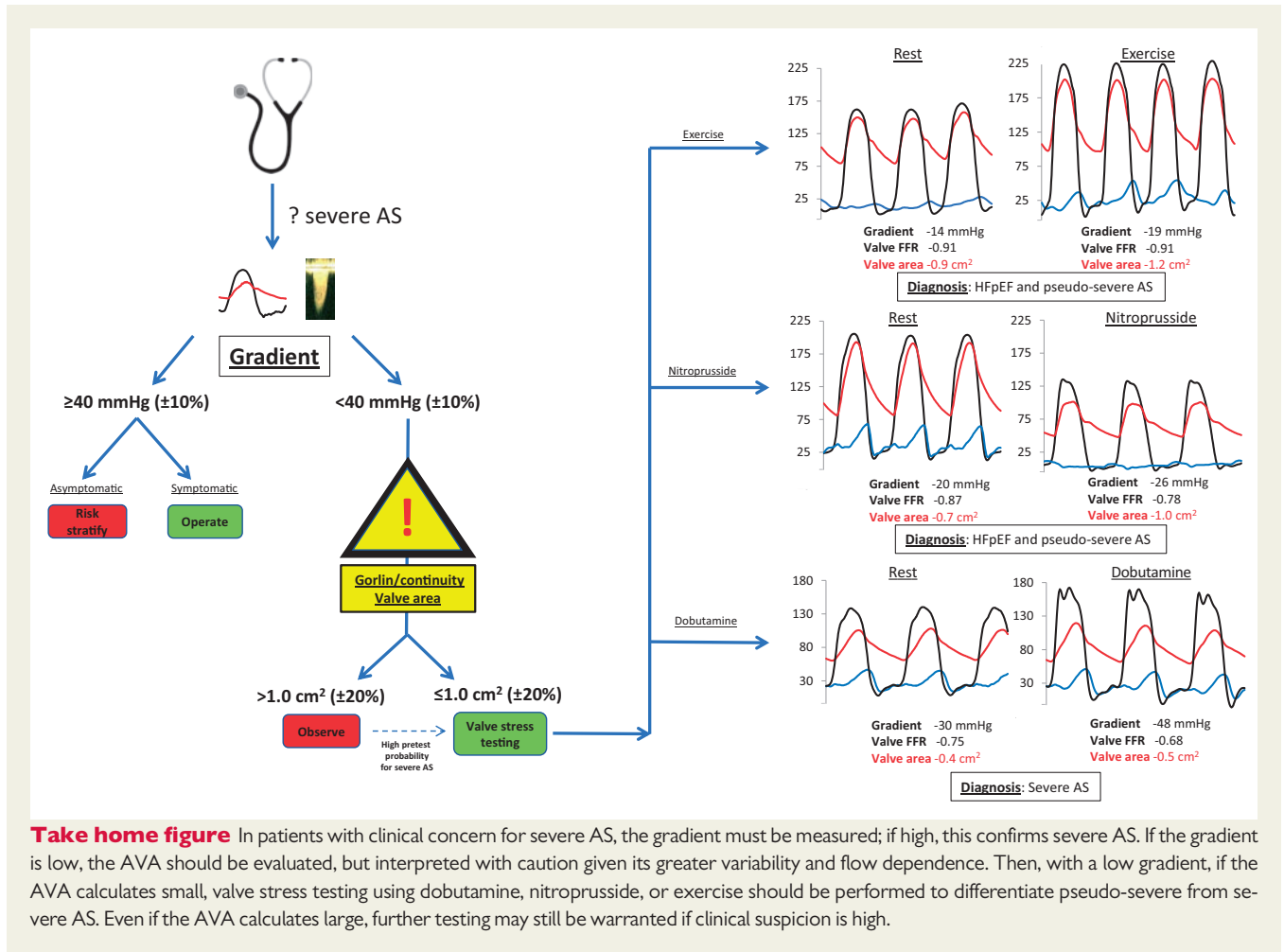
Take home figure In patients with clinical concern for severe AS, the gradient must be measured; if high, this confirms severe AS. If the gradient is low, the AVA should be evaluated, but interpreted with caution given its greater variability and flow dependence. Then, with a low gradient, if the AVA calculates small, valve stress testing using dobutamine, nitroprusside, or exercise should be performed to differentiate pseudo-severe from severe AS. Even if the AVA calculates large, further testing may still be warranted if clinical suspicion is high.

This is a landmark study with meticulous high-fidelity, dynamic measurements in truly severe AS with far-reaching implications. Most importantly, the authors demonstrate that current steady-state resistance models (including the Gorlin AVA) are poorly representative of the impact of AS on flow dynamics in patients with known severe AS. The authors also clearly show that no resting haemodynamic parameter may predict what occurs during the stress of exercise, when the patients become symptomatic. The other very important and novel finding was the linear relationship between pressure gradient and flow once a prosthetic valve was deployed, suggesting that normally functioning leaflets do not contribute a valvular impedance load. Therefore, a normally functioning prosthetic valve behaves like a pure resistor load with a narrowed orifice but normal leaflet excursion as would be explained by Ohm's law. This in itself has important implications for our understanding of patient–prosthesis mismatch where prosthetic valves, depending on effective orifice size, probably provide a constant steady-state, non-pulsatile pressure load to the ventricle in the aortic position.[9]

Clinical implications

What are the clinical implications that we can apply based upon this discussion? If properly obtained by either catheterization or Doppler echocardiography, the transvalvular mean gradient is a reproducible direct measurement without assumptions, which has been shown to be predictive of outcome; several studies have demonstrated poorer outcome with AS gradients ≥40 mmHg (but not consistently with a low AVA).[10,11] The guideline definition of 'severe' valve disease is the degree at which symptoms may occur and prognosis becomes poorer; thus, patients with gradients ≥40 mmHg have severe AS. The teachings of Bernoulli centuries ago did show a direct relationship of gradient and flow; thus, in low-flow states, the transvalvular gradient will fall and there may still be severe AS with lower gradients. However, it is clear that the current assessment of AS severity by calculation of the AVA is based upon multiple assumptions that may not hold in clinical practice, explaining both frequent clinical discordance and its inconsistent prognostic significance.[6,10,11] Therefore, we should not look upon the AVA as a 'gold standard' for AS severity. A small AVA of ≤1.0 cm^2 alone should not be used as a single parameter for the diagnosis of severe AS; instead it should be a 'warning' to clinicians that in patients with lower gradients, severe AS may still be present.

In these patients with low gradients of <40 mmHg and AVA ≤1.0 cm^2, further evaluation is then required to determine the true severity of the AS as well as the effect of the valve on the myocardium and filling pressures. The authors have provided definitive data demonstrating that predicting how the aortic valve behaves under

stress-related increased flow (which is what determines exertional symptoms) is not possible from resting measures. They also conclusively show that given the limitations underlying the AVA calculation, stress-related measurement is probably best assessed using either the stress-related pressure gradient or the ratio of absolute pressures, as opposed to changes in AVA. We and others have shown that in these patients with low-flow, low-gradient AS and preserved ejection fraction, there are frequently two resistors in series—one from the stenotic aortic valve and one from increased peripheral vascular resistance as many patients have concomitant systemic hypertension.[12] If lowering the blood pressure reduces the total load on the left ventricle enough to normalize left ventricular filling pressures, simple medical therapy may be enough to relieve symptoms. Thus further evaluation of the gradient, output, and filling pressures by changes in haemodynamic status by either dobutamine, nitroprusside, or even exercise would be of great utility in determining the optimal approach to these patients (*Take home figure*). We should also point out that there is intrinsic variability in any physiological measurement in cardiovascular diseases. Therefore, clinicians should not rely on single 'cut-off' values but instead take into consideration the known variability of these measurements (up to ±10% with direct gradient measurements and more than ±20% for AVA).

Finally, it also bears mention that the original natural history studies of severe AS, which have greatly influenced our clinical practice, were based purely on clinical assessment[13] or peak velocity,[10,11,14,15] and not on Gorlin-calculated valve areas. We must acknowledge that some practices get passed down and entrenched through the generations and are rarely questioned, such as the Gorlin valve area. Johnson *et al.*, through a thought-provoking study, elegantly remind us that we must incessantly challenge our current practice patterns with rigorous new data, so we can continuously improve the care of our most vulnerable patients.

Funding

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